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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/941,471	08/29/2001	Gang Liu	6724.US.P1	7987

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EXAMINER
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OH, TAYLOR V

ART UNIT	PAPER NUMBER
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1625

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/941,471

**Applicant(s)**

LIU ET AL.

**Examiner**

Taylor Victor Oh

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 11 March 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-75 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 71-75 is/are rejected.
- 7) ☒ Claim(s) 1-70 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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The Status of Claims

Claims 1-70 have been objected.

Claims 71-75 have been rejected.

Applicant's arguments with respect to claims 1-75 ,which do not have the heterocyclic pro-drug containing various heterocycles , have been considered but are moot in view of the new ground(s) of rejection.

Claims 1-9, 11, 14-19, 22, 25, 30-35, 40-44, 49, 50-52, 55-58, 61-67, and 70-75, drawn to the heterocyclic pro-drug containing various heterocycles withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to the nonelected group II, there being no allowable generic or linking claim. Election was made **without** traverse on 2/21/03.

Applicants are reminded of removing any claimed limitation related to any heterocyclic compounds throughout the claims 1-75. The non-hetero-compounds can be allowed with the proviso that all the heterocyclic compounds have been removed throughout the claims 1-75.

Claims 1-70 have been objected due to applicants' failure to separate the non-hetero-compounds from the hetero compounds.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

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person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 71-75 are rejected under 35 U.S.C. 112, first paragraph , because the specification, while being not enabling for treating disorders caused by overexpressed or altered protein tyrosine phosphatase 1B by administering the compound of formula I for any known disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are directed to not the specific diseases, but all kinds of the diseases by using the mechanistic nature of inhibiting protein tyrosine phosphatase 1B. The specification falls short because data essential for treating many diseases by means of inhibiting protein tyrosine phosphatase 1B is not described in the specification.

In In re Wands, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention in claims 71-75 is the method for treating disorders caused by overexpressed or altered protein tyrosine phosphatase 1B by administering the compound of formula I, thereby treating numerous diseases, for example, type I and II diabetes, obesity, autoimmune disorders, acute and chronic inflammatory disorders, osteoporosis, cancer, malignant disorders.

The claim 75 sets forth the treatment of cancer and malignant disorders generally. However, there never has been a compound capable of treating cancer generally. There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. Even the most broadly effective antitumor agents are only effective against a small fraction of the vast number of different cancers known. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-1), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms. Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

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When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Ferens*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs Novo Nordisk*, 42 USPQ2d 1001, 1006.

### **The State of the Prior Art**

The state of the prior art is in the followings:

PTP1B has been identified as at least one of the major phosphatases involved in the IRTK regulation through studies conducted both *in vitro* (Seely *et al. Diabetes* 45: 1379-1385 (1996)) and *in vivo* using PTP1B neutralizing antibodies (Ahmad *et al. J. Biol. Chem.* 270: 20503-20508 (1995)). Two independent studies have indicated that PTP 1B knock-out mice have increased glucose tolerance, increased insulin sensitivity and decreased weight gain on a high fat diet (Elchebly *et al. Science* 283: 1544-1548 (1999) and Klamann *et al. Mol. Cell. Biol.* 20: 5479-5489 (2000)). Overexpression or altered activity of tyrosine phosphatase PTP1B can contribute to the progression of various disorders, including insulin resistance and diabetes (*Ann. Rev. Biochem.* 54: 897-930 (1985)). Furthermore, there is evidence which suggests inhibition of protein tyrosine phosphatase PTP1B is therapeutically beneficial for the treatment of disorders such as type I and II diabetes, obesity, autoimmune disorder, acute and chronic inflammation, osteoporosis and various forms of cancer (*J. Natl. Cancer Inst.* 86: 372-378 (1994); *Mol. Cell. Biol.* 14: 6674-6682 (1994); *The EMBO J.*, 12: 1937-1946 (1993); *J. Biol. Chem.* 269: 30659-30667 (1994); and *Biochemical Pharmacology* 54: 703-711(1997)).

However, no selective or nonselective inhibitor of PTP1B has been approved for treating any disease in any animal.

### **The predictability or lack thereof in the art**

The instant claimed invention is highly unpredictable as discussed below:

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It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In *re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that inhibiting the PTP1B would result in only the specific site involved in IRTK regulation and neutralizing antibodies; this kind of treatment can not translated to all the possible treatment of any disease in regards to their therapeutic effects.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by the compounds of formulas I, and the inhibition of the PTP1B, one of skill in the art is unable to fully predict possible results from the administration of the claimed compounds of formula I due to the unpredictability of the role of inhibiting the PTP1B, i.e. whether promotion or inhibition would be beneficial for the treatment of the diseases.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

**The amount of direction or guidance present**

The direction present in the instant specification is that the compounds of formula I can inhibit the PTP1B which helps in the treatment for type I and II diabetes, obesity, autoimmune disorders, acute and chronic inflammatory disorders, osteoporosis, cancer, malignant disorders. However, the specification is silent and fails to provide guidance as to whether the diseases listed (pages 2-3 and 11) require the inhibition of the PTP1B for treatment, i.e. the specification fails to provide a correlation between the diseases listed and the inhibition of the PTP1B. Also, there is no direction and guidance for the inhibition of the PTP1B for the treatment of any kinds of diseases.

**The presence or absence of working examples**

There is no working example for the treatment of type I and II diabetes, obesity, autoimmune disorders, acute and chronic inflammatory disorders, osteoporosis, cancer, malignant disorders. Furthermore, there are not other working examples for any other diseases listed in the specification. Also, the compounds which are disclosed in the specification have no pharmacological data regarding the treatment of any other disease besides inhibitory activity of the PTP1B using compounds from various classes and have no data on the possible treatment of the various diseases that require the inhibitory activity of the PTP1B. Also, the specification fails to provide working examples as to how the listed diseases can be treated by the inhibition of the PTP1B, i.e. again, there is no correlation between the diseases listed and inhibition of the PTP1B.



**The breadth of the claims**

The breadth of the claims is that the compounds of formula I can treat any disease by the inhibition of the PTP1B, without regards as to the affect of the inhibition of the PTP1B on the stated diseases.

**The quantity of experimentation needed**

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what listed diseases would be benefited by the inhibition of the PTP1B and would furthermore then have to determine whether the claimed compounds would provide treatment of the disease by the inhibition of the PTP1B.

**The level of the skill in the art**

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compounds of formula I for the treatment of any disease by the inhibition of the PTP1B . As a result, necessitating one of skill to perform an exhaustive search for which diseases can be treated by the compounds of formula I in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that “ a patent is not a hunting license. It is not a reward for search , but

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compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taylor Victor Oh whose telephone number is 571-272-0689. The examiner can normally be reached from 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Mckane can be reached on 571-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

\*\*\* *[Signature]*  
5/31/94

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